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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,861	11/01/2001	Johan Ericson	21882-502	6942

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,861	ERICSON, JOHAN	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *25-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/3/03, 01/09/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

VC

DETAILED ACTION

Applicant's response filed on 01/13/05 has been acknowledged.

Claims 1-71 are pending.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Election/Restrictions

Applicant's election with traverse of Group I claims 1-24, wherein the elected subject matter is **stem cell differentiation**, Groucho co-repressor protein **Grg4** and Groucho interacting protein **Nkx2.2** in the reply filed on 01/13/05 is acknowledged. The traversal is on the ground(s) that searching the differentiation of stem cells along with progenitor cells, peripheral nervous system cells, interneurons, motor neurons, dopaminergic neurons, cortical neurons, GABAergic neurons, and glutaminergic neurons would not pose any serious burden on the office. The applicant furhter argues that the Groucho co-repressor proteins Grg1, Grg2, Grg3, Grg4 are expressed together naturally therefore there is no serious search burden to examine all Groucho co-repressor proteins as single invention. The applicant argues that the Groucho interacting protein selected from the Nkx-family including Nkx2.2, NKx2.9, NKx6.1 and NKx6.2 are closely related structures with overlapping functions therefore there is no serious search burden to examine all Groucho interacting proteins as single invention. This is not found persuasive because the role of each Groucho co-repressor proteins (Grg1, Grg2, Grg3, Grg4) and Groucho interacting protein (Nkx2.2, NKx2.9, NKx6.1 and NKx6.2) in the differentiation of stem cells, progenitor cells, peripheral nervous system cells, interneurons, motor neurons, dopaminergic neurons, cortical neurons, GABAergic neurons, and glutaminergic neurons, a cell of the peripheral nervous system, a kidney cell, a heart muscle cell, a pancreatic cell, a skin cell, a liver cell, and a white or red

blood cell is distinct, since each cellular micro environment is distinct having different differentiation pathways eliciting different modes of operation functions and effects. Thus these inventions are distinct and are of separate uses.

The requirement is still deemed proper and is therefore made FINAL.

Claims 25-71 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 01/13/05.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the fate of differentiation of a chicken neural stem cell into a ventral neuron, by introducing into the neural stem cell nucleic acid encoding the Nkx2.2 gene which upon expression forms complexes with Grg4, does not reasonably provide enablement for a method of guiding the fate of differentiation of any other cell type by contacting the cell with any other Groucho-interacting proteins which forms complexes with any Groucho-corepressor proteins in-vitro or in-vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

The instant invention relates to a method of guiding the fate of differentiation of a cell.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of instant invention encompasses a method of guiding the fate of differentiation of any type of stem cell, wherein the stem cell differentiates into any and all kinds of cells founds in any animal (i.e. neuronal cells, muscle cell, skin cell, kidney cell, heart muscle cell, pancreatic cell, liver cell, white or red blood cell etc). In addition the scope of invention as claimed also encompasses the differentiation of any developed cell like, muscle cell, skin cell, kidney cell, heart muscle cell, pancreatic cell, liver cell, white or red blood cell etc. into a specific cell type, wherein the resulted specific cell type has not been defined by any phenotypic traits.

At best the specification teaches that NKx2.2 interacts with Grg4 using an in-vitro immunoprecipitation assay (Spec page 74). However, the specification as filed fails to disclose that NKx2.2 is also capable of binding to any other Groucho-corepressor proteins, especially Grg1, Grg2 or Grg3. Similarly the specification fails to disclose that Grg4 is also capable of binding to the any other Groucho-interacting protein selected from all proteins having a TN-like domain, all proteins having a homeodomain, class I proteins like Pax, Dbx and Irx etc and class II polypeptide including all Nkx-family members especially NKx2.9, Nkx6.2, Nkx6.3, etc. In addition the specification fails to disclose that interaction of all Groucho-interacting proteins with any and all Groucho-corepressor protein is capable of guiding the fate of differentiation of any kind of cell into a specific cell type, wherein the cell is any stem cell, progenitor cell or any differentiated mature cell.

The specification further teaches in-ovo (chicken) electroporation of cDNA encoding NKx2.2 gene (Spec page 75). The specification further teaches that the expression of NKx2.2 modulates the fate of ventral neurons during embryonic development (spec page 81, lines 2-31, example-V, fig-3A). The specification teaches that NKx2.2 interacts with Grg4 using an in-vitro immunoprecipitation assay (Spec page 74). The specification further teaches that in chickens Grg4 is expressed at uniform

levels at early neural plate and neural fold stages. But after neural tube closure, Grg4 is expressed in a graded manner, with a higher level of expression in ventral and intermediate regions of the neural tube (Spec. page 85 lines 4-6). However the specification as filed fails to disclose that contacting any kind of cell with any Groucho-interacting protein would differentiates in to a specific cell type (as claimed). Specifically the specification fails to disclose that expression of polypeptide encoded by SEQ ID NO:7, SEQ ID NO:13 and SEQ ID NO:14 would guide the fate of differentiation of any kind of mature cell or a stem cell. Furthermore SEQ ID NO:7 and SEQ ID NO:14 are hypothetical proteins without any biological activity that would guide the fate of differentiation of a cell (any type) to a specific cell type. Furthermore, the specification fails to disclose that the formation of complex between NKx2.2 and Grg4 would guide the fate of differentiation of any other cell type (besides neuronal stem cells) in-vitro or in-vivo wherein in the cells are contacted with NKx2.2 using any and all means (i.e. genetic transfection or protein administration). In addition the specification fails to disclose that contacting the undifferentiated neuronal stem cells in-vivo with NKx2.2 expression vector or NKx2.2 protein is capable of guiding the fate of differentiation to a particular neuronal phenotype like interneuron, a motor neuron or a Projection neuron selected from a dopaminergic neuron, a cortical neuron, a gaba-ergic neuron and a glutnminergic neuron.

State Of Art And Predictability:

The state of the art at the time of filing teaches that differentiation of neurons from the neuronal stem cell is complex and relies on the interaction of multiple signaling pathways such as Sonic Hedgehog, Wnts, and BMPs and their antagonists (Placzek et al Nat Rev Neurosci. 3:230-40. 2005). Furthermore the role of Sonic Hedgehog signaling during vertebrate development is complex because the differentiation and maintenance of distinct cell types is thought to be controlled by inductive signals acting at different concentration thresholds. The degree of receptor activation in response to these signals is a known determinant of cell fate, but the later steps at which graded signals are converted into all-or-none distinctions in cell identity remain poorly resolved. For example in the ventral neural tube, motor neuron and interneuron generation

depends on the graded activity of the signaling protein Sonic hedgehog (Shh) see Briscoe et al Nature. 398(6728):622-7, 1999, Briscoe et al EMBO, 4(8):761-765, 2003. The instant invention as claimed requires the formation of complex between any Groucho-interacting proteins and any Groucho-corepressor protein, which is considered highly unpredictable in the state of cell differentiation art. The state of the art at the time of filing teaches that Gro/TLE proteins have no intrinsic DNA binding activity but can be targeted to specific gene regulatory regions due to their ability to interact with variety of different DNA-binding transcription factors. It has been postulated that Gro/TLE family proteins probably repress transcription by multiple mechanisms but many aspects of Gro/TLE protein function remain to be explored, including the possible post-translational regulation of Gro/TLE activity as well as the mechanisms by which Gro/TLE proteins direct repression at a distance (Chen et al, Gene 249:1-16, 2000). Therefore considering the state of the art and limited amount of guidance provided in the instant specification it is highly unpredictable that contacting any cell (undifferentiated or differentiated) with any Groucho-interacting protein would guide the fate of its differentiation to a specific cell type. For example, considering the applicant's disclosure it is unclear how one skilled in the art would guide the fate of differentiation of any non-neuronal cell (undifferentiated or differentiated) without further undue amount of experimentation. In addition it would be highly unpredictable that one would be able to guide the fate of differentiation of a mature neuronal cell (i.e. neuron) to any specific cell type (i.e. a muscle cell). Similarly without any enabling disclosure it is highly unpredictable that any cell would differentiate into an insulin producing beta cell by contacting cells with any Nkx gene or gene product. Similarly without any enabling disclosure it is highly unpredictable that any cell would differentiate into interneuron, a motor neuron or a Projection neuron selected from a dopaminergic neuron, a cortical neuron, a gaba-ergic neuron and a glutnminergic neuron.

The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the

circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case guiding the fate of differentiation of any cell (differentiated or un differentiated) to any cell type (related or unrelated) by contacting the cell with any Groucho-interacting protein via any and all means is not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the cell" in 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 is indefinite because it is unclear what are the metes and bound of the claim limitation "a specific cell" in this context.

Claim 1 is indefinite because it is unclear what are the metes and bound of the claim limitation "alternative pathways of differentiation" in this context.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300.**

Sumesh Kaushal
Examiner GAU 1636

SUMESH KAUSHAL
PATENT EXAMINER